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Colloid-amyloid Bodies in PUVA-treated Human Psoriatic Patients

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In 4 cases of PUVA-treated psoriatic patients a number of colloid bodies and amyloid-like deposits were seen at the dermo-epidermal junction, in a very similar fashion the colloid bodies and the amyloid substances are deposited in lichen planus and in primary cutaneous amyloidoses respectively. In some instances such deposition was found within the epidermis and contained remnants of cellular debris. Serial sections revealed that a part of the intraepidermal deposit is located in the dermis. Some deposition is partially composed of typical amyloid filaments and partially of nonamyloidal filaments. The latter were identical to those found in colloid or Civatte bodies of lichen planus and other conditions. Follow-up biopsies done in 1 patient several months after the cessation of the treatment still showed these substances. It was suggested that the amyloid-like substances are the product of special degeneration (apoptosis) of epidermal cells as colloid substances: Initially these cells undergo filamentous or colloid degeneration and they drop off into the dermis; where some of the characteristics of filaments are modified and connective tissue elements are added to produce such filamentous and amorphous components as seen in the amyloid island, whereas others remain as colloid bodies. Absorption or elimination of these substances seem to be extremely slow.

In the course of electron microscopic studies on Psoralen-UVA (PUVA) treated psoriatic skin [1], we found a number of keratinocytes undergoing filamentous (colloid or hyaline) degeneration, particularly in the vicinity of melanocytes. Some of these cells were still within the confinement of the basal lamina, whereas others were already dropped into the upper dermis. In both cases straight, nonbranching amyloid-like filaments of 60–70 Å were seen admixed with thicker, wavy filaments of colloid degeneration.

While the origin of colloid bodies has been more or less agreed upon i.e.: that they derive from dropped-off epidermal cells [2, 3, 4], the origin and mode of formation of amyloid in primary cutaneous amyloidoses have been quite controversial [5–16].

Amyloid of primary cutaneous amyloidoses such as lichen amyloidosus [5, 17], macular amyloidosis [6] and amyloid deposition associated with skin tumors [7, 8] seems to be unrelated to systemic immunoglobulin abnormalities [5, 7, 8]. Amyloid deposition in these conditions is limited in the vicinity of the epithelial tissue, namely in the dermoepidermal junction [5, 6, 17] or in the stroma of tumors [7, 8]. Initial deposition of amyloid resembles collagen islands [2, 17] but it also resembles epithelial cells in size and configuration.

Amyloid deposition was found surrounded by cell membrane [5]; this was interpreted as an evidence of intracellular production of amyloid [5]. Amyloid-like filaments were described in association with epidermal keratinocytes [9, 17–19]. These previous findings allowed a speculation that skin amyloid might be an abnormal product of the epidermis. However, no direct evidence has been presented.

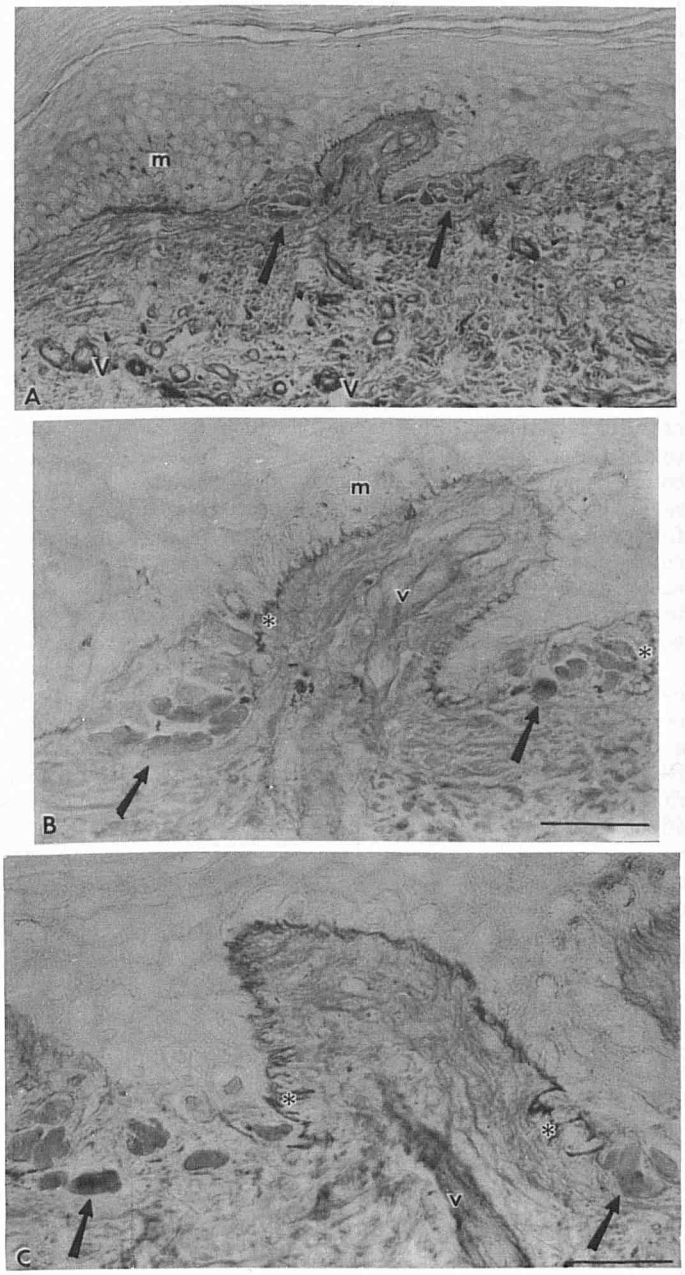

FIG 1. PUVA-treated lesion (total: 197 Joules over an 8-mo period). PAS stain after diastase. Flattened epidermis contains an increased melanosomes (*m*). In the upper dermis aggregations of PAS-positive, diastase resistant bodies (*arrows*) are seen. Perivascular coat of PAS-positive, diastatase resistant substance (*V*) is also prominent. PAS-positive round bodies (*arrows*) are seen either above the basement membrane (*) or below it (1*B*, 1*C*) (1*A* reduced from × 109 and 1*B* and 1*C* reduced from × 175). Scale = 100 μm each.

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Lichenoid and macular amyloidoses are common among orientals [20, 21] and Puerto Ricans [6]. The lesions of macular amyloidosis clinically show rippled hyperpigmentation and histologically show incontinence of melanosomes; this phenomenon may be related to degenerative changes of melanosome-containing keratinocytes or even melanocytes. Of particular interest in this regard is a recent report that amyloid deposition similar to that of lichenoid or macular amyloidosis was found in the lesion of incontinentia pigmenti achromians [22] and in depigmented lesions of a patient with macular amyloidosis [23]. In this condition it is known that melanocytes undergo degenerative changes [24]. A close association of amyloid deposit with epidermal melanocyte has been demonstrated [5].

Finally, morphological similarity between colloid bodies and amyloid islands was emphasized by Black and Wilson-Jones [25]; significantly, in both conditions reduction is noted in the number of DOPA-positive melanocytes in the lesion. Nagao and Iijima [26] and Ebner and Gebhart [27] previously recorded an association of colloid bodies with amyloid deposit. McDonald, Black and Remnarain [16] have recently mentioned a similar observation of their own.

Despite many pieces of circumstantial evidence of a close interrelationship between colloid and amyloid, no one has so far demonstrated co-existence of both in one body of deposition. PUVA-treated skin provided a unique opportunity to follow this problem.

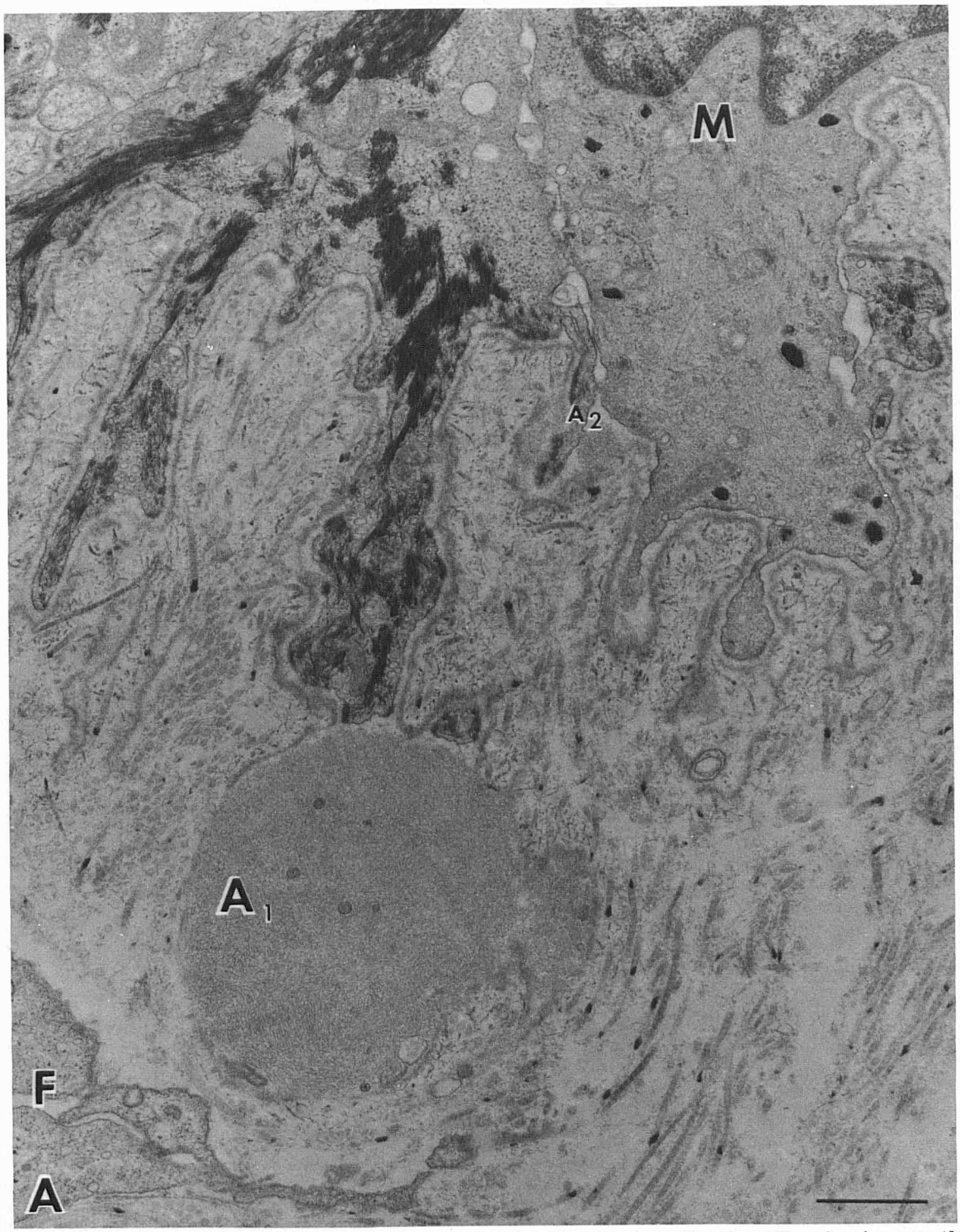

FIG 2, *A*. A round ball-like filament aggregation (A_1) is about to drop into the dermis. A fibroblast (*F*) and melanocyte (*M*) are in the neighborhood of this aggregation. A small aggregation (A_2) is seen just beneath the melanocyte (see Fig 5*A*) (× 17,500). Scale = 1 μm.

MATERIALS AND METHODS

Six white psoriatic patients used in this study were previously described [1]. Briefly, they received, before the biopsies, total doses of UVA peaking at 365 nm ranging from 41 to 197 Joules over 8 mo. They were treated twice a week 2 hr after 40 mg of 8 methoxypsoralen (8-MOP), except for a short induction period when smaller doses of 8-MOP were administered in each treatment. Biopsies were taken from the leg, shoulder, lower back and buttocks with 4-mm skin punch and processed routinely for electron microscopy [1, 2, 5]. Sun-exposed areas were avoided for biopsies. Biopsies were taken both from the previously involved areas and uninvolved areas. By the time specimens were taken, the psoriatic lesions were completely flattened and clinically indistinguishable from the normal skin. Biopsies were performed 72 to 96 hr after the last treatment to avoid acute changes of irradiation. There was marked uniform hyperpigmentation but neither lichenification nor rippled hyperpigmentation similar to those of lichenoid or macular amyloidosis.

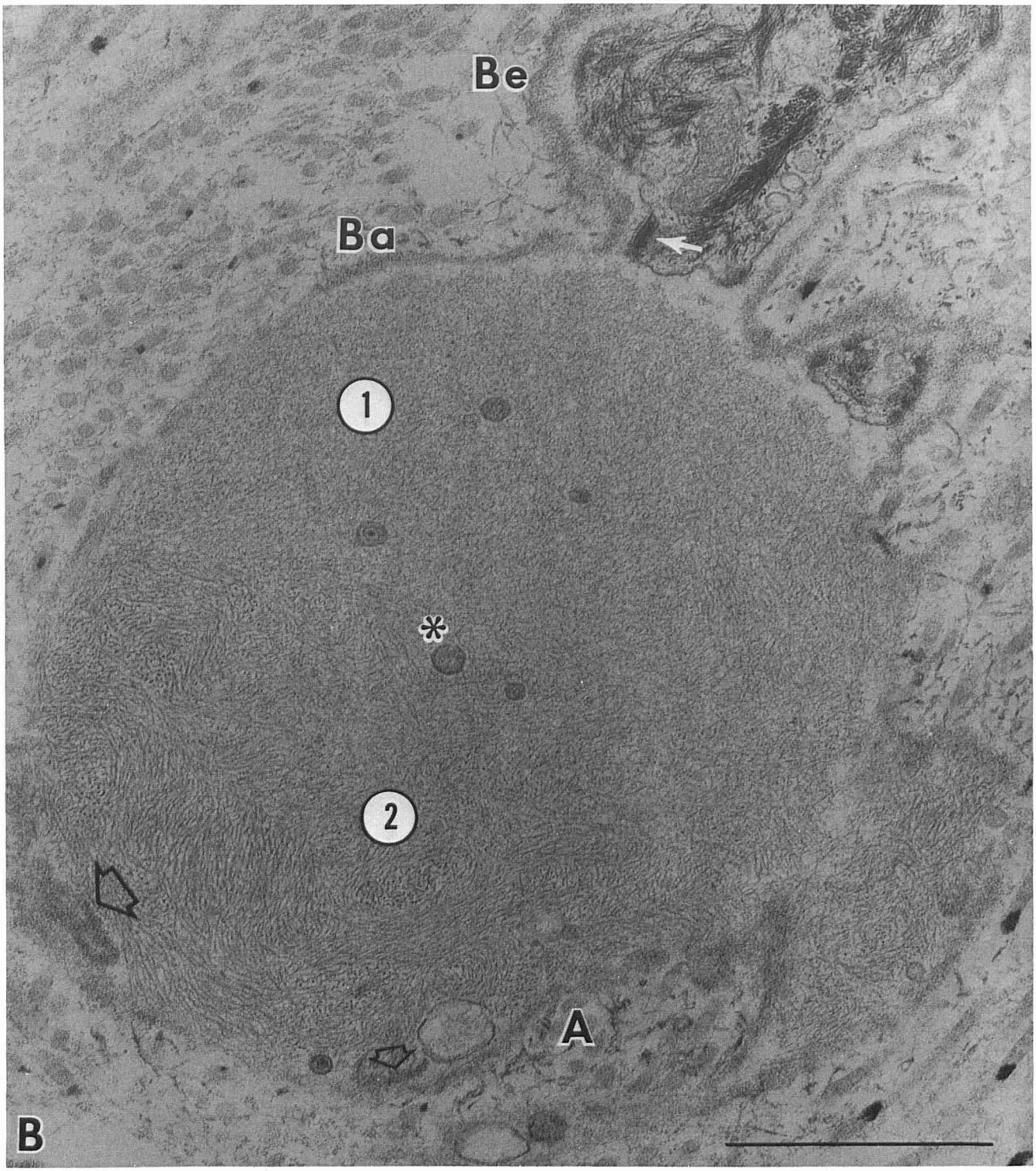

FIG 2, *B*. High magnification of filament aggregation shown in Fig 1*A*. It is seen that this aggregation is surrounded by almost uninterrupted basal lamina (*Ba*) which is continuous with the basal lamina of the epidermis (*Be*). The presence of anchoring fibrils (*A*) and half desmosome-like structures (*hollow black arrows*) indicates that *Ba* is a part of *Be,* which was stretched by the dropping off of this filament aggregation. Remnants of cytoplasmic organelles (*) are seen. The upper half of this aggregation (*1*) has relatively thin, straight filaments, whereas the lower half has thicker, wavy filaments (2) often forming whorls. *Solid white arrow:* intact half desmosome of a basal cell (× 45,000). Scale = 1 μm.

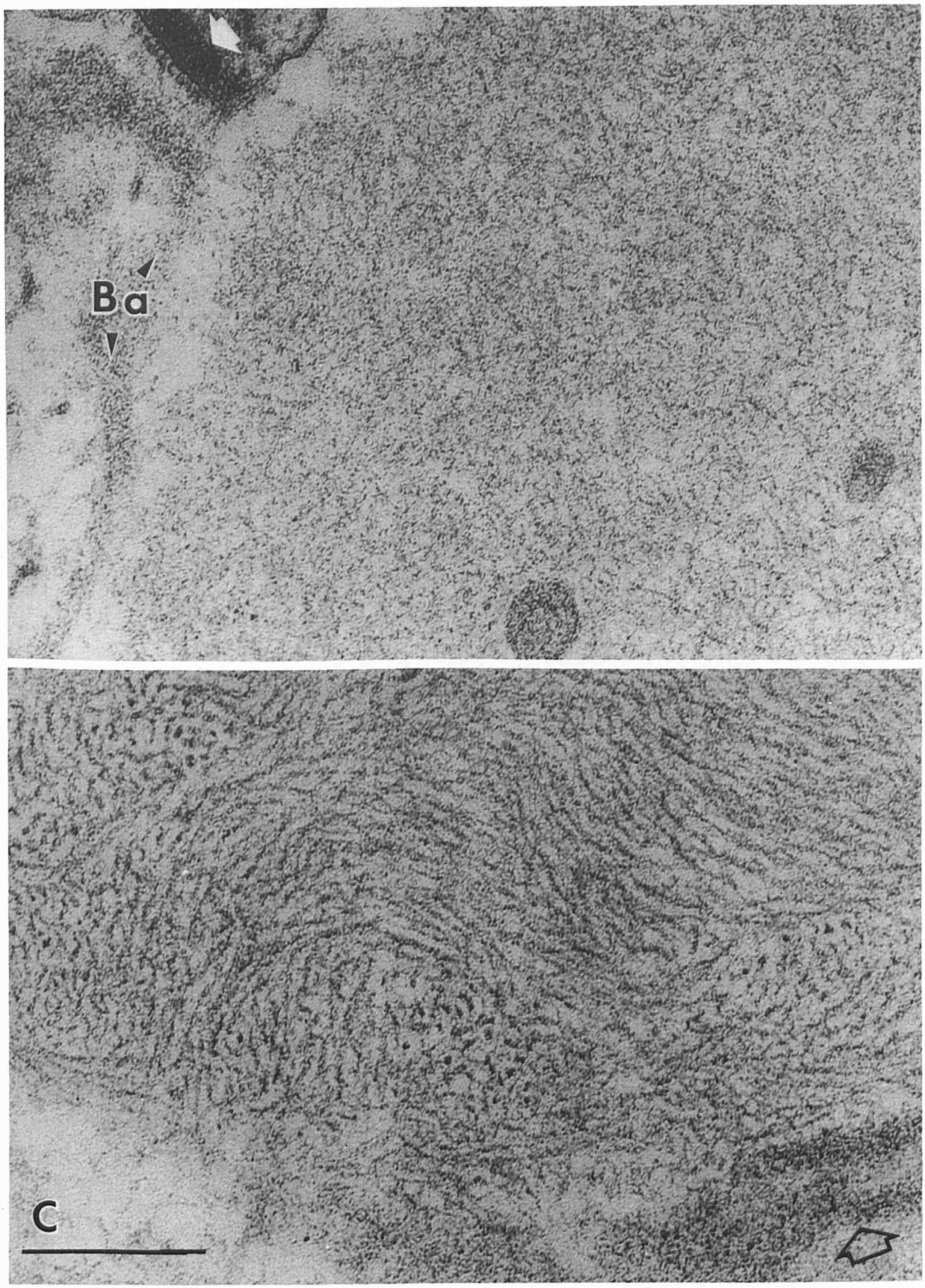

FIG 2, *C.* Enlargement of the upper and lower parts of this aggregation to the same magnification reveals that the former (*upper picture*) consists of 60–70 Å straight filaments whereas the latter (*lower picture*) consists of 60–80 Å wavy filaments. *Ba:* basal lamina. *Solid white arrow:* half desmosome of a basal cell. *Hollow black arrow:* Degenerated half desmosome (× 160,000). Scale = 0.2 μm.

One patient continued the same schedule of treatment for 6 more mo (total of 481 Joules) and stopped the treatment for 4 mo; before he resumed the treatment biopsies were taken from the involved and noninvolved buttocks, adjacent to previous biopsy sites.

Specimens from clinically normal skins and psoriatic lesions were taken from each patient before the treatment and used as controls. Other controls were run using the specimens taken from the skin of normal volunteers who were repeatedly exposed to UVA (345 nm) over a period of 1 yr with total doses of 1900 and 2600 Joules/cm^2. The details of methodology of this experiment have been published elsewhere [28].

One half of each specimen used for electron microscopy was processed routinely for H & E stain, PAS stain, alkaline congo red stain, crystal violet stain and others.

RESULTS

In the dermal-epidermal junction of 3 cases of PUVA-treated normal skin as well as PUVA-treated lesions, aggregations of

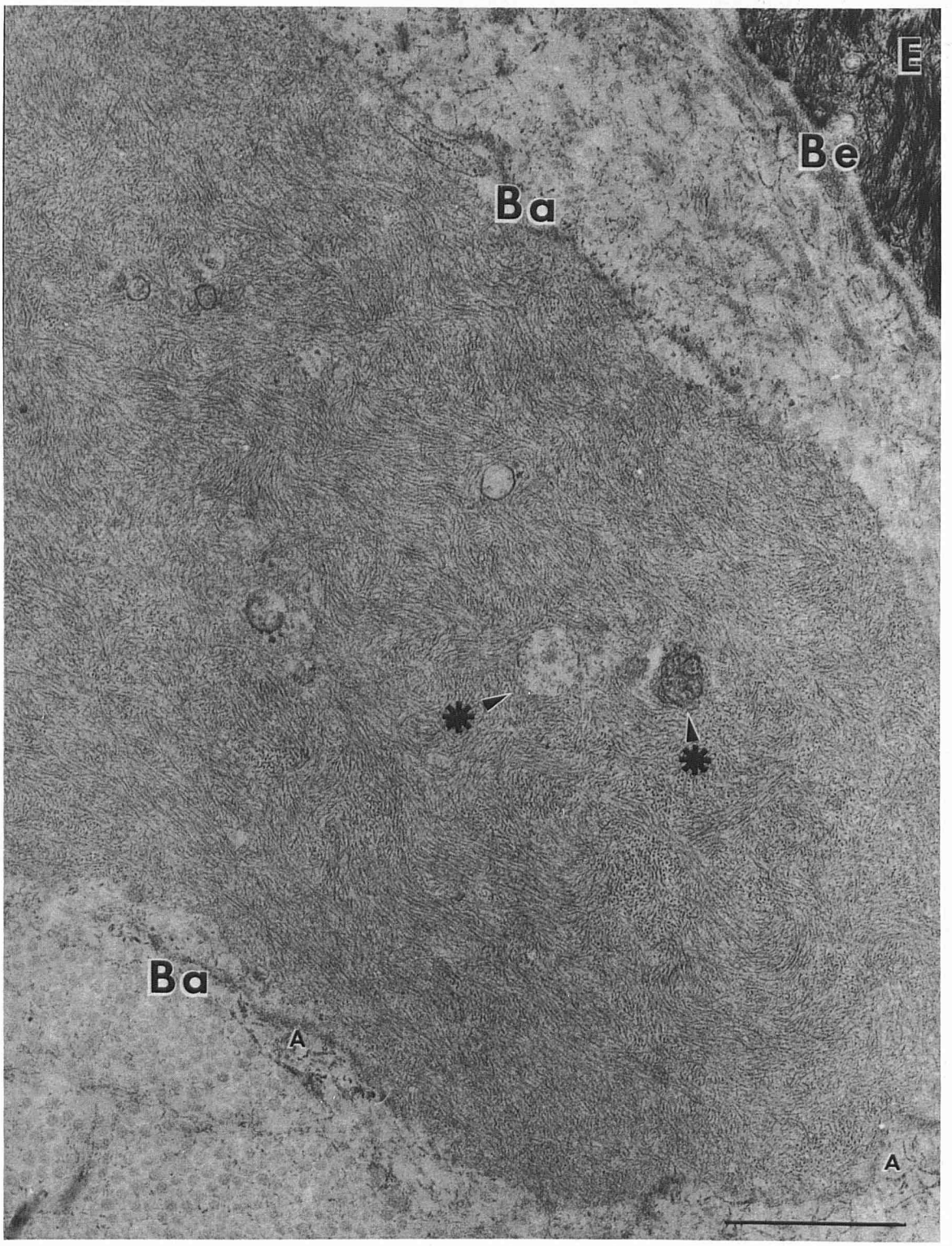

FIG 3. This aggregate is located subepidermally and surrounded by interrupted basal lamina (*Ba*) which is also abutted by anchoring fibrils (*A*). Degenerated cytoplasmic organelles (*) are contained. The majority of filaments are of the wavy, whorlforming type. *Be:* basal lamina of the epidermis. *E:* epidermis (× 30,000). Scale = 1 μm.

PAS-positive, diastase-resistant bodies were seen (Fig 1*A*, 1*B*, 1*C*). Alkaline Congo red stain and crystal violet stain (metachromasia) were occasionally positive in these bodies. With electron microscopy, aggregations of filaments were resolved in these bodies. On one type, the aggregation was seen either above the basal lamina or surrounded by it, namely, located within the epidermis (Fig 2*A*, 2*B*, 2*C*). In the other type, it was found separated from the basal lamina of the epidermis, but still surrounded partially with the basal lamina of their own (Fig 3). In still another type of aggregation, usually situated deeper in the dermis, no basal lamina enveloped it (Fig 4*A*, 5*A*). In serial sections, it was found that some aggregations were partially within the epidermis (Fig 2*A*) and partially separated from it (Fig 6*A*). In some instances an aggregation was found in the vicinity of healthy melanocytes (Fig 6*A*). Many melanocytes were closely associated with all 3 types of aggregation (Fig 2*A*, 4*A*, 5*A*, 6*A*). Fibroblasts or histiocytic cells were also closely situated (Fig 2*A*, 4*A*, 5*A*, 6*A*).

In higher magnification it was seen that when the basal lamina surrounded these aggregations, it was abutted by a number of anchoring fibrils (Fig 2*B*, 3, 6*A*).

There were two kinds of filaments in these aggregations: The first type was 60–80 Å in diameter; these were wavy, branching and anastomosing. These tended to form whorls and thus very much resembled fibrils found in Civatte bodies or hyaline bodies of lichen planus and other conditions [2–4]. The second type of filament was slightly thinner (60–70 Å); these were nonbranching, nonanastomosing and more straight (Fig 2*B*, 2*C*, 4*B*, 5*B*, 6*B*). These filaments, therefore, qualified themselves to be called amyloid filaments as observed in primary localized cutaneous amyloidoses [5–8, 17] as well as in systemic amyloidosis [29].

In some aggregations a mixture of these 2 types was seen (Fig 2*B*, 6*B*). For example in Fig 2*B* and 6*B* the upper one-half of the aggregation was "amyloid" and the lower one-half was "colloid." Such aggregation was often surrounded by a basal lamina which was continuous with the basal lamina of the epidermis (Fig 2*B*). Remnants of cytoplasmic organelles were scattered throughout such aggregations (Fig 2*B*). Half desmosome-like structures were often detected at the periphery of these aggregations (Fig 2*B*, 6*A*). No aggregations of filaments were found in the control skins, namely, normal skin and psoriatic lesions of all three cases biopsied before the treatment.

The specimens biopsied from a patient who received more than 400 Joules over 1 yr contained an increased number of similar bodies in the upper dermis in spite of the resting period of 4 mo (Fig 7*A*, 7*B*, 7*C*). These bodies are also composed of colloid-like wavy filaments of 60–80 Å (Fig 7*C*) and amyloid-like straight filaments of 60–70 Å (Fig 7*B*). They also contained debris of cellular organelles (Fig 7*B*, 7*C*).

DISCUSSION

Although an absolute identification of the material found in this study with one of the known amyloid requires further

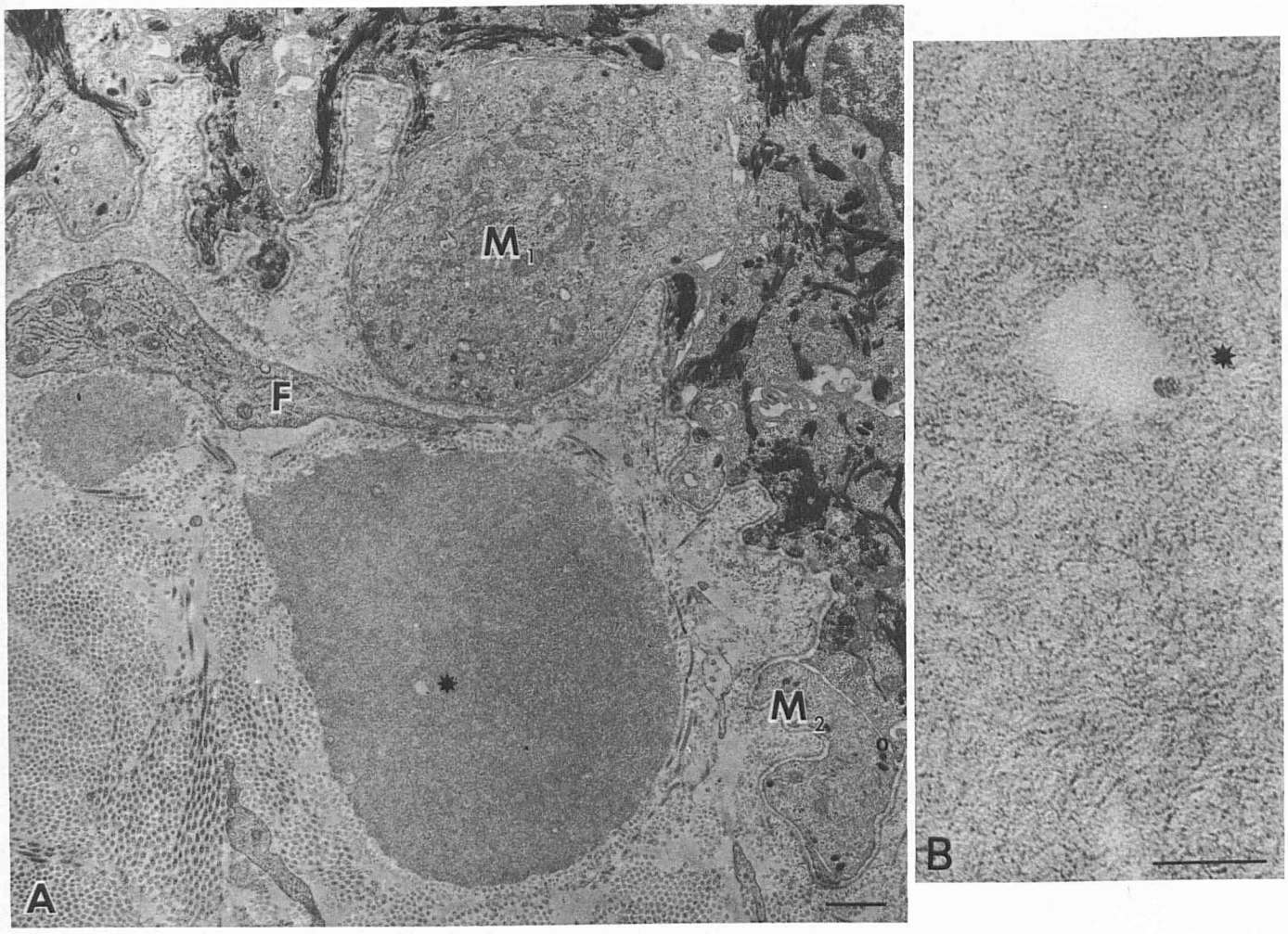

FIG 4, *A*. Two aggregations are separated from the epidermis by a fibroblast (*F*). These are not enclosed by a basal lamina. Two melanocytes (M_1, M_2) are seen nearby. *: the area to be enlarged in Fig 4*B* (reduced from × 2,000). Scale = 1 μm. 4*B*. The majority of filaments are short, straight amyloid filaments with beadings. Individual filaments measure 60–70 Å in diameter. *: reference to Fig 4*A* (reduced from × 115,500). Scale = 0.2 μm.

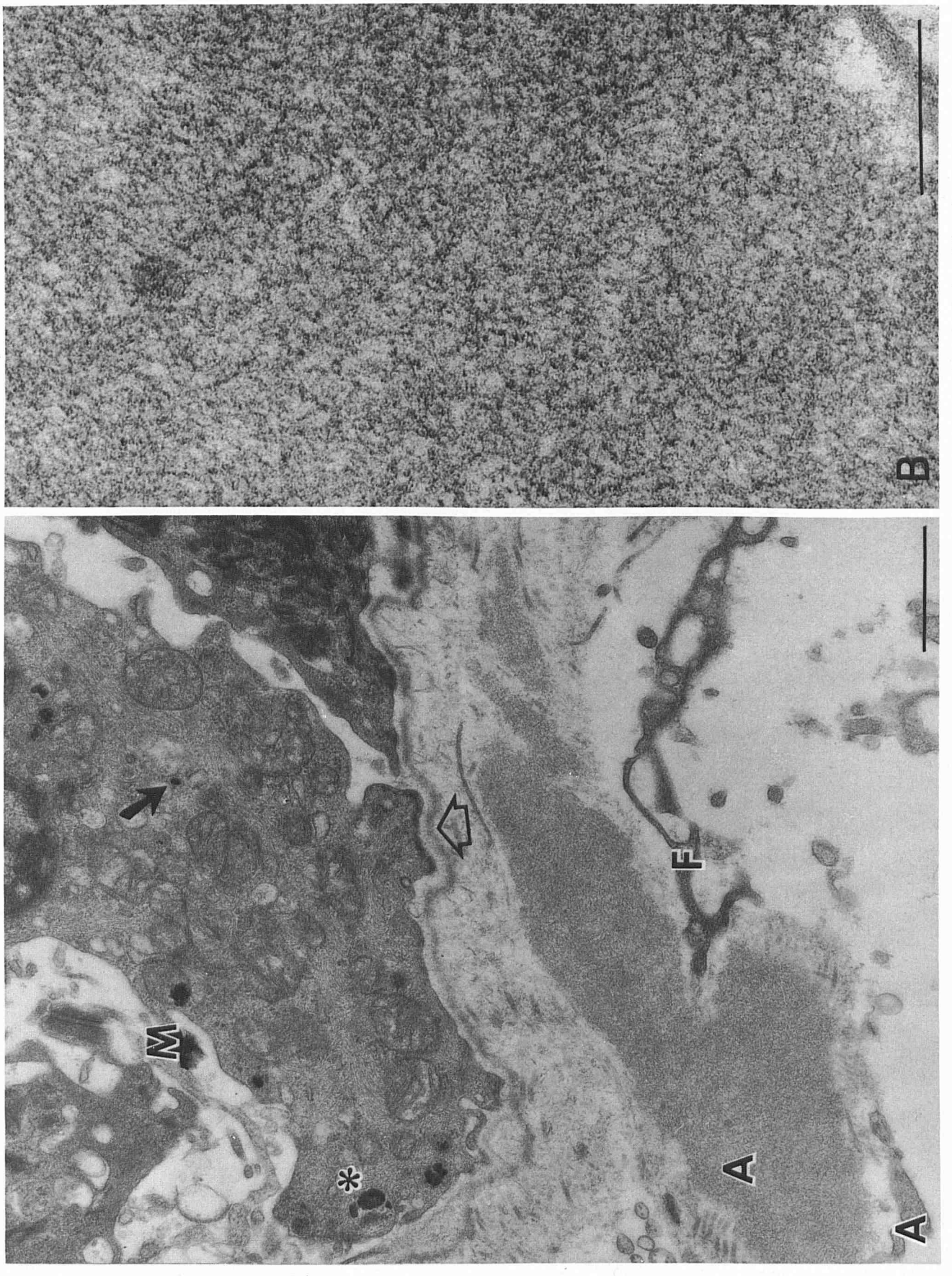

FIG 5, *A*. Aggregation (*A*) of amyloid type filaments (see Fig 5*B*) is seen just beneath a melanocyte (*M*). After stimulation, this melanocyte autophagocytosed its own melanosomes (*); this cell has half desmosomes (*hollow arrow*) and individual melanosomes (*solid arrows*). Notice that a fibroblast (*F*) is surrounding this aggregation (reduced from × 23,000). Scale = 1 μm. 5*B*, High magnification of the area labeled *A* in Fig 5*A* reveals straight, amyloid-type filaments. Compare with wavy-type filaments in Fig 2*C* (reduced from × 160,000). Scale = 0.2 μm.

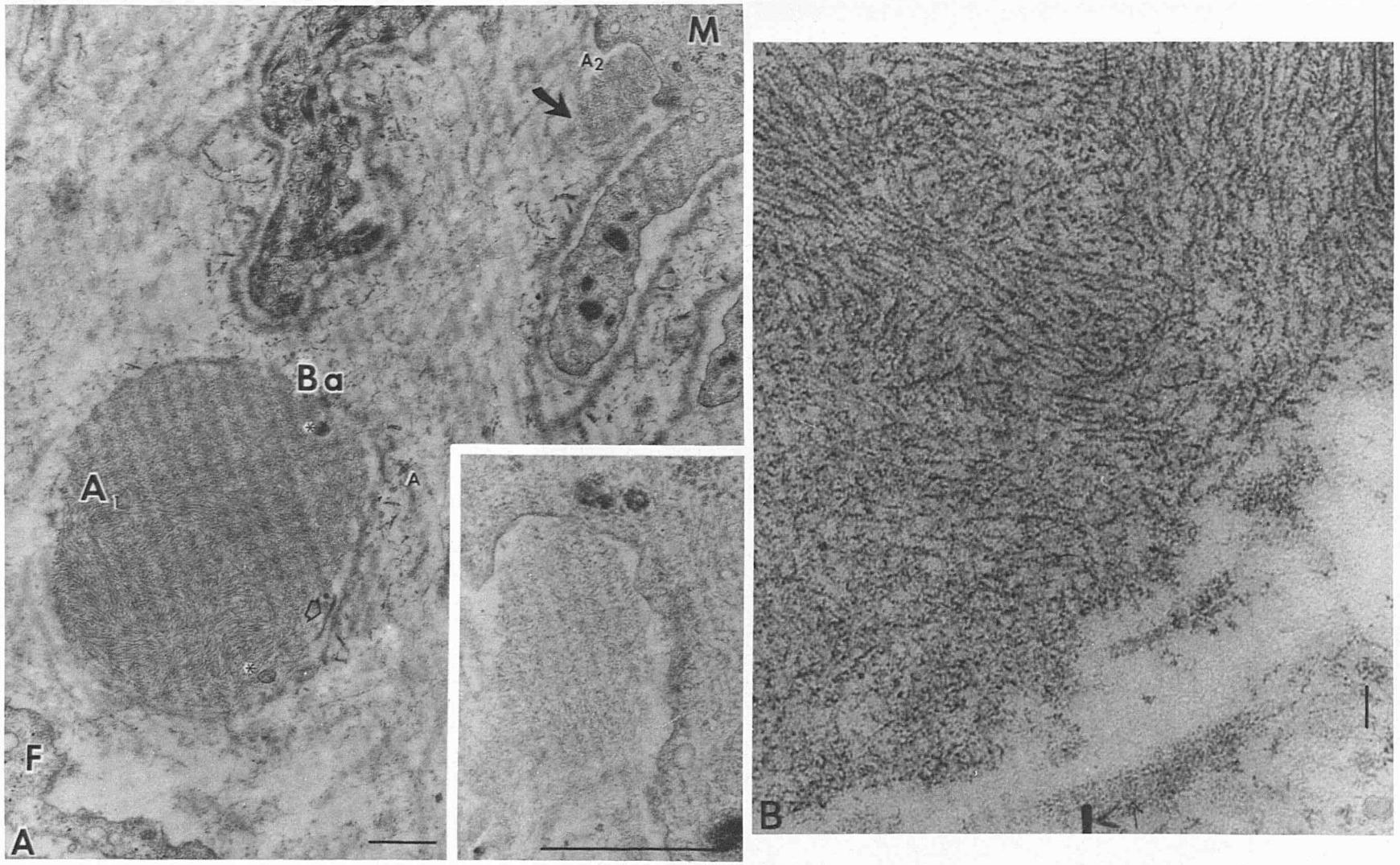

FIG 6, *A*. One of the sections cut serial to Fig 2*A*. A ball-like aggregation (A_1) is now separated from the epidermis but still enveloped with basal lamina (*Ba*). Anchoring fibrils (*A*) abut upon the basal lamina. Remnants of cytoplasmic organelles (*) and a half-desmosone (*hollow arrow*) can be recognized in this aggregation. A small aggregation (A_2) is situated beneath the same melanocyte (*M*) as shown in Fig 2*A*. It is spilling into the dermis (*solid arrow*). Further serial sectioning (*insert*) did not reveal any direct connection of this aggregation to this melanocyte. A_1 is composed of half amyloid-type and half Civatte body-type wavy filaments, whereas A_2 is mainly amyloid filaments (reduced from × 30,000 and *insert*, reduced from × 77,500). Scale = 0.5 μm each. *B*, The area labeled A_1 in Fig 6*A* is enlarged. Amyloid filaments are seen in the lower left, while wavy filaments occupy the upper right (reduced from × 160,000). Scale = 0.2 μm.

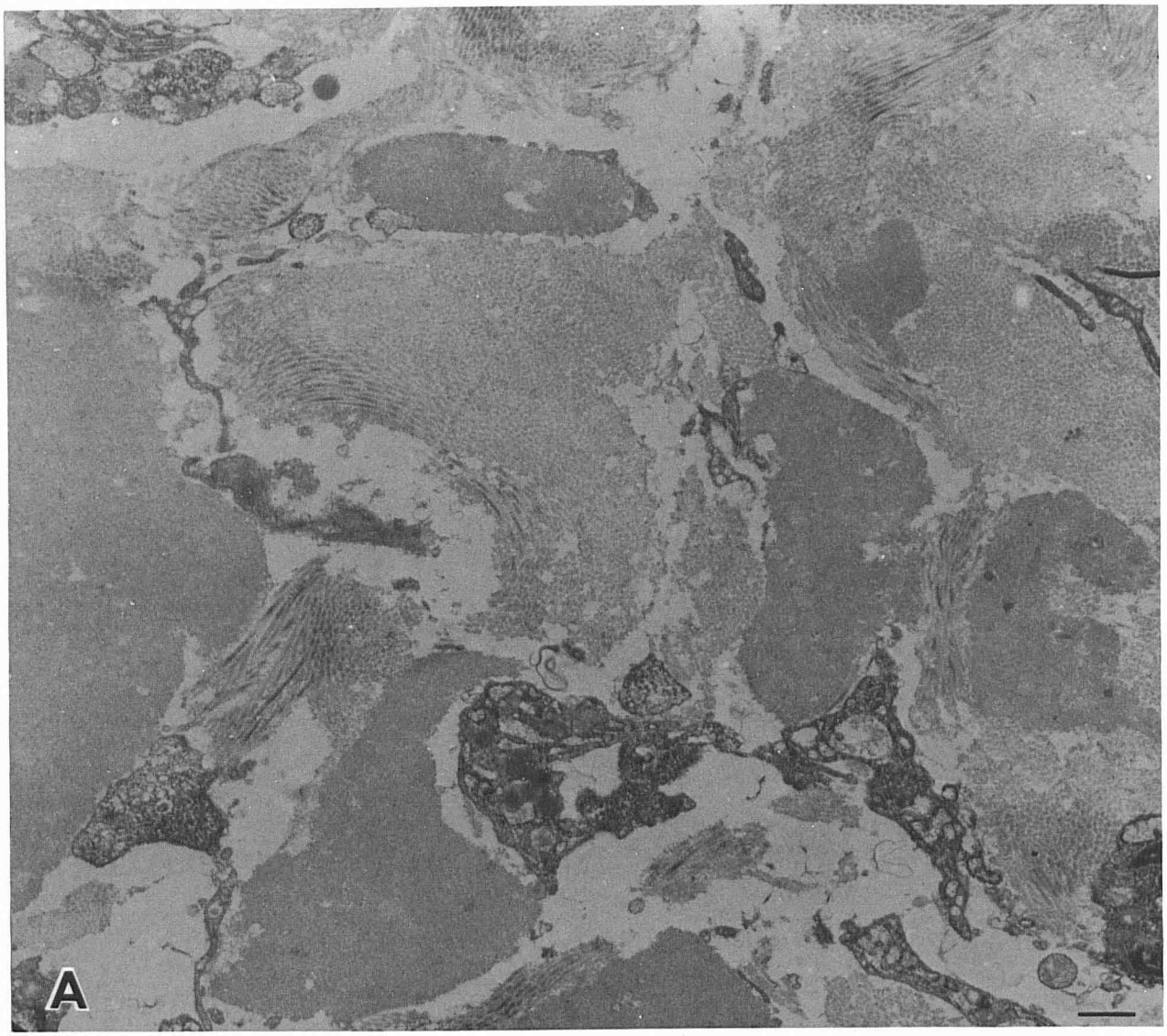

FIG 7, *A*. Colloid-amyloid bodies are increased in number after long-term PUVA therapy (total: 481 Joules over a 18-mo period) and located deeper than those found in comparatively short-term therapy (Fig 1–6). Psoriatic lesion (× 8,000). Scale = 1 μm.

studies using biochemical and immunological methods, at least the ultrastructure and histochemical characteristics of the material satisfy the criteria of amyloid. Therefore, we call it amyloid-like.

In contrast to colloid bodies of lichen planus, the colloid-amyloid bodies produced by PUVA-therapy apparently do not elicit infiltration of small mononuclear cells to the epidermal-dermal junction. In this respect, they are similar to amyloid deposition in primary cutaneous amyloidoses such as lichenoid and macular amyloidoses. Another similarity is the chronicity of deposition: Amyloid deposition lasts several years and colloid-amyloid bodies were found several months after the interruption of the PUVA treatment. In other human studies done in our laboratories [30] UVA alone was found to produce these bodies and they persisted in the skin when biopsies were taken months after the cessation of the irradiation.

Finding of an hybrid between colloid body and amyloid island in PUVA-treated psoriatic patients suggested that cutaneous amyloid could derive from the epidermal cells. It is assumed that (i) epidermal keratinocytes (and possibly melanocytes also) first undergo filamentous degeneration by an apoptotic process [2–4] which was induced by UVA, PUVA or chronic dermatitis; (ii) filamentous degeneration produces relatively thick, wavy, filaments such as those seen in lichen planus (Civatte bodies) and/or produces amyloid or amyloid precursors; (iii) degenerated cells lose basal lamina coverage and drop into dermis; and (iv) dermal components are added to these filaments and the final product "amyloid" emerges. If the above presumption is correct, this hypothesis explains several enigmas surrounding the primary localized cutaneous amyloidosis; (i) the absence of systemic gammopathy in the patients; (ii) a very pruritic neurodermatitis-like lesion overlying the amyloid deposition, causing primary damage to the epidermal cells; (iii) reticular or rippled hyperpigmentation in macular amyloidosis due to dropping off of melanin-containing keratinocytes and melanocytes; and (iv) isolated deposition of amyloid in the vicinity of cutaneous epithelial tumors such as actinic keratosis [7], basal cell epithelioma and cylindroma [8].

In lichen amyloidosus, amyloid-like filaments were described in the epidermis or in keratinocytes [25–27]. However, most of these filaments were wavy type, except a few instances [17]. In the present study, an admixture of wavy type filaments and amyloid filaments in one degenerated cell as well as dropping off of amyloid-containing apoptotic cells in serial sections were documented for the first time.

Our control studies showed that UVA alone does induce apoptosis [30]. Amyloid-producing apoptotic cells may be induced in greater number by a combination of UVA and psoralen

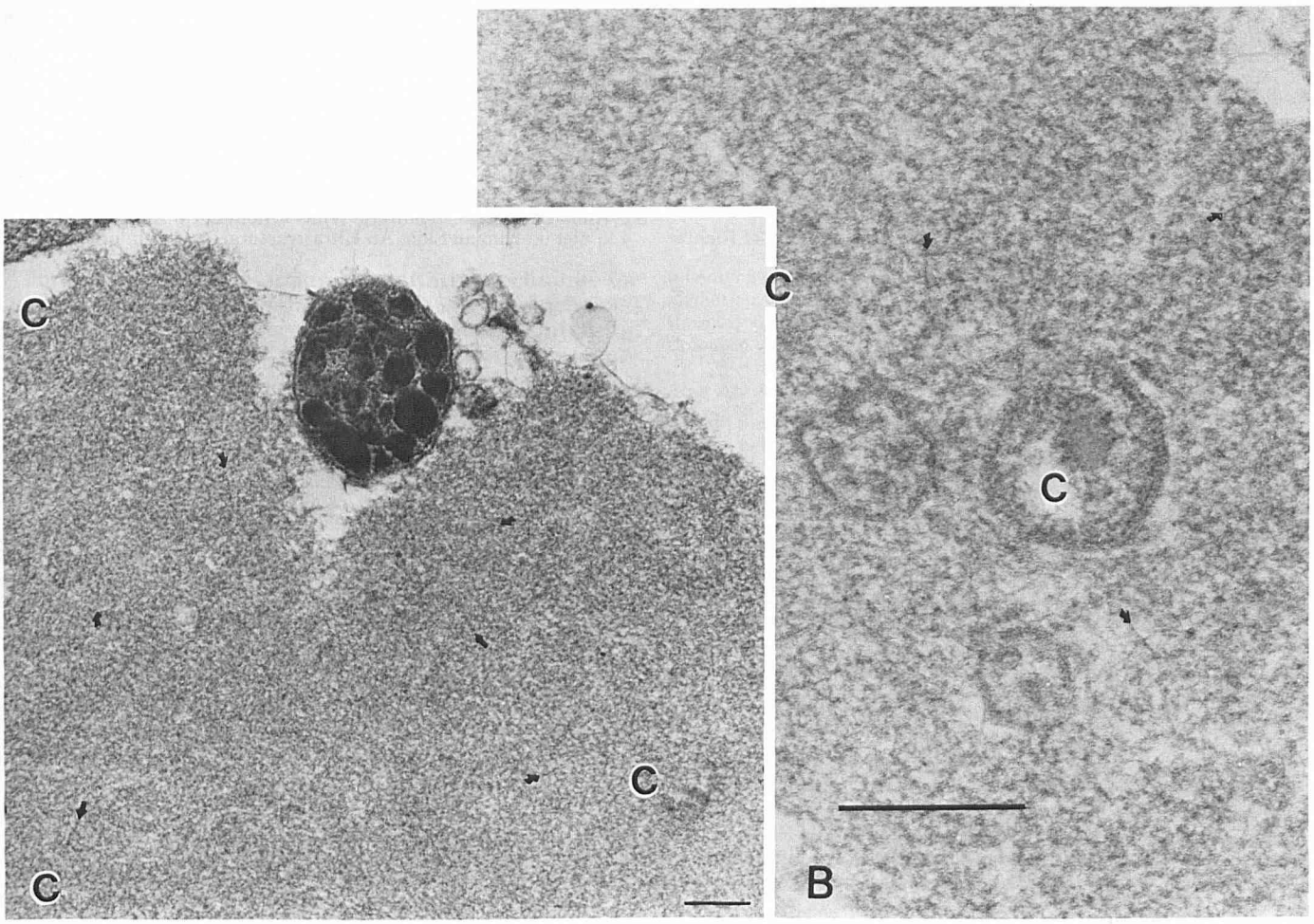

FIG 7, *B*. An admixture of wavy filaments, straight filaments (*arrows*), amorphous substance and cellular debris (*C*) found in the lesion treated for 18 mo with a total of 481 Joules. (reduced from × 160,000). Scale = 0.2 μm. 7, *C*. Admixture of wavy and straight (*arrows*) filaments and melanosomes within a limiting membrane: This suggests that this body has derived from apoptotic keratinocytes or melanocyte in which autophagositosis of its own melanosomes took place (Fig 5*A*). Same specimen as used in Fig 7*B*. *C*: cellular debris (reduced from × 55,000). Scale = 0.2 μm.

which is conjugated to pyrimidine based by UVA and interferes with DNA metabolism. As mentioned above, not every apoptotic cell becomes amyloid, neither does every patient treated with the same PUVA regimen produce colloid-amyloid. Therefore, a combination of a special type of damage to the epidermal cells and optimal dermal environment in a susceptible individual seem to be required.

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Announcement

The Epidermis in Disease, an International Symposium, sponsored by the European Society for Dermatological Research will be held April 18–20, 1979, at the Welsh National School of Medicine, Heath Park, Cardiff. The program is divided into 6 sessions as follows:

April 18

Session A: Pharmacological Aspects of Epidermal Disease
M. Greaves, Institute of Dermatology, London (Chairman) J. J. Voorhees (Michigan); H. Maibach (San Francisco); K. Halprin (Miami); F. Marks (Heidelberg); C. E. Orfanos (Koln); P. J. A. Holt (Cardiff)

Session B: Epidermal Symbionts
M. Prunieras, Universite de Paris VII, France (Chairman) B. Falck (Lund); L. Juhlin (Uppsala); G. Stingl (Vienna); G. Szabo (Boston); S. S. Bleehen (Sheffield); J. A. A. Hunter (Edinburgh); Mrs. G. Moreno (Paris); A. Breatnach (London)

April 19

Session C: Disorders of Keratinization
R. Marks, Welsh National School of Medicine, Cardiff (Chairman) P. Elias (San Francisco); A. Breathnach (London); I. Anton-Lamprecht (Heidelberg); C. Skerrow (Glasgow); I. A. King (Birmingham); W. J. Cunliffe (Leeds); G. Plewig (Munchen); C. E. Orfanos (Koln); R. Caputo (Milan)

Session D: Reaction Patterns of Epidermal Disease
E. Wilson Jones, Institute of Dermatology, London (Chairman) P. Elias (San Francisco); J. M. Lachapelle (Bruxelles); E. Christophers (Kiel); R. Marks (Cardiff); H. Honigsmann (Innsbruck); H. H. Wolff (Munchen); W. E. Parish (Beds.)

April 20

Session E: Epidermopoiesis in Disease
E. Christophers, University of Kiel, W. Germany (Chairman) C. Potten (Manchester); S. Gelfant (Georgia); E. B. Laurence (London); K. Halprin (Miami); N. Wright (Oxford); J. J. Voorhees (Michigan); M. G. Davies (London)

Session F: Immunopathology of Epidermal Disease
E. Beutner, State University of New York at Buffalo, U.S.A. (Chairman) S. Jablonska (Warsaw); A. Langner (Warsaw); S. Katz (Bethesda) R. Mackie (Glasgow); K. Holubar (Wien); T. P. Chorzelski (Warsaw); L. Fry (London

Registration forms can be obtained by contacting the co-organizers: Dr. R. Marks, Department of Medicine, Welsh National School of Medicine, Heath Park, Cardiff. CF4 4XN or Prof. E. Christophers, Department of Dermatology, University of Kiel, 2300 Kiel, W. Germany.